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Metal triflate catalyzed highly regio- and stereoselective 1,2-bromoazidation of alkenes using NBS and $TMSN_3$ as the bromine and azide sources

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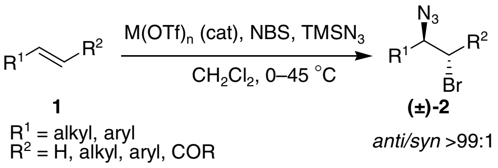
Abstract—Metal triflate catalyzed 1,2-bromoazidation of alkenes was performed using *N*-bromosuccinimide (NBS) and trimethylsilyl azide ($TMSN_3$) as the bromine and azide sources, respectively. Among the metal triflates, $Zn(OTf)_2$ was found to be the best catalyst. This catalytic process represents a highly regioselective, stereoselective and high yielding method for the synthesis of *anti*-1,2-bromoazides from a variety of alkenes including α,β-unsaturated carbonyl compounds.

1,2-Functionalization of alkenes with azide and halogens (haloazidation) represents an important transformation in organic synthesis. These vicinal haloazide compounds are versatile precursors of vinyl azides,[1] amines,[2] heterocycles[3] and particularly aziridines.[4] The study of highly regioselective and stereoselective haloazidation of alkenes still remains an important and challenging task for organic chemists.

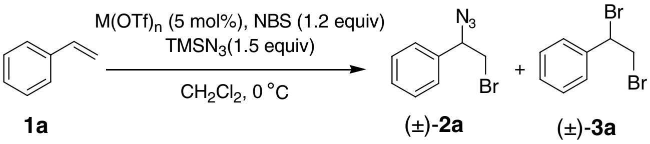
In the literature, vicinal 1,2-iodoazides are prepared by addition of I_2/AgN_3,[5] ICl/NaN_3,[6] $PhI(OAc)_2/Et_4NX/TMSN_3$,[7] $CAN/NaI/NaN_3$,[8] $IPy_2BF_4/TMSN_3$[9] and $Oxone/wet\text{-}Al_2O_3/KI/NaN_3$[10] onto the alkenes, mostly under noncatalytic conditions. Poor *anti*/*syn*-selectivity is a significant limitation of these processes. The instability of these iodo-compounds is an additional problem.

1,2-Bromoazidation of alkenes was first reported by Hassner and Boerwinkle[11] by the addition of bromine azide generated from bromine and sodium azide, which required the use of excess hydrazoic acid to suppress the formation of dibromo compounds. Krief[4] described the bromoazidation of alkenes by in situ generated bromine azide from NBS and NaN_3 in aqueous solution. Hydrolysis is the major problem in this reaction. Later, Olah et al.[12] reported the bromoazidation of 1,2-disubstituted- and trisubstituted alkenes with NBS and $TMSN_3$ catalyzed by superacidic Nafion-H



Scheme 1.

Table 1. Screening of metal triflates as catalysts for the bromoazidation of **1a** with NBS and $TMSN_3$



Entry	ML_n	*t* (h)	**2a**:**3a**[a]	Yield of **2a**[b] (%)
1	None	12	50:50	30
2	$La(OTf)_3$	6	>95:5	74
3	$Y(OTf)_3$	4	>95:5	55
4	$Yb(OTf)_3$	2	>95:5	45
5	$Sm(OTf)_3$	10 min	>95:5	65
6	$Cu(OTf)_2$	10 min	Mixture of products	
7	$Zn(OTf)_2$	10 min	>95:5	85

[a] Ratio determined from the ^1H NMR spectrum of the crude reaction mixture.
[b] Isolated yields of pure **2a** after column chromatography.

Keywords: Metal triflate; Catalyst; Bromoazidation; *N*-Bromosuccinimide (NBS); Trimethylsilyl azide ($TMSN_3$); Alkenes; α,β-Unsaturated carbonyl compounds; *anti*-1,2-Bromoazides.

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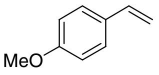
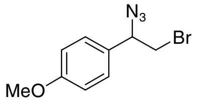
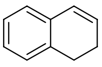
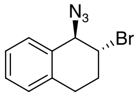
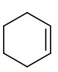
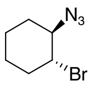
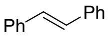
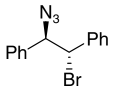
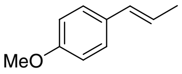
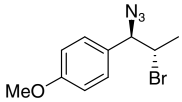
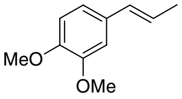
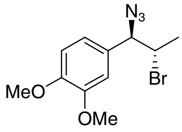
resin, however, there was no reaction with terminal alkenes. In this letter, we report a highly regio- and stereoselective bromoazidation of various alkenes catalyzed by metal triflates with NBS and $TMSN_3$ as the bromine and azide sources, respectively (Scheme 1).

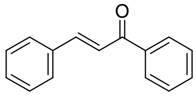
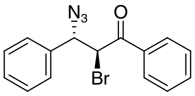
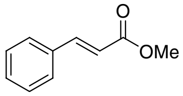
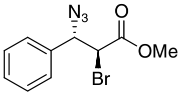
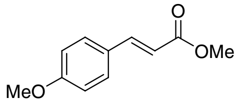
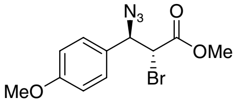
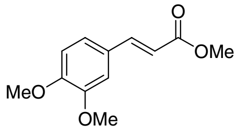
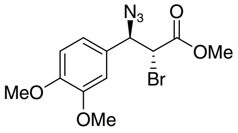
Our continued efforts[13] to provide new catalytic methods for the regio- and stereoselective 1,2-halofunctionalization of alkenes led us to anticipate that a suitable Lewis acid might catalyze the 1,2-haloazidation of alkenes with NBS and $TMSN_3$. We screened different Lewis acid as catalysts, in particular metal triflates, and styrene **1a** was selected as a model substrate (Table 1). Among the metal triflates studied, $Zn(OTf)_2$ was found to be the best catalyst with $Sm(OTf)_3$ being comparable. It should be noted that in the absence of Lewis acid, **1a** re-

Table 2. $Zn(OTf)_2$ catalyzed bromoazidation of alkenes with NBS and $TMSN_3$

Entry		Alkene	*t* (min)		Product	*Anti*:*syn*	Yield[a] (%)
1	**1b**		10	(±)-**2b**		—	72
2	**1c**		30	(±)-**2c**		>99:1	85
3	**1d**		30	(±)-**2d**[b]		>99:1	80
4	**1e**		60	(±)-**2e**		>99:1	92[c]
5	**1f**		20	(±)-**2f**		>99:1	75
6	**1g**		20	(±)-**2g**		>99:1	70

[a] Isolated yields of pure **2** after column chromatography.
[b] Ref. 7.
[c] Combined isolated yield of **2e** and 30% of the dibromo compound which could not be separated.

Table 3. $Zn(OTf)_2$ catalyzed bromoazidation of α,β-unsaturated carbonyl compounds with NBS and $TMSN_3$

Entry		Alkene	*t* (h)		Product	Yield[a] (%)
1	**1h**		15	(±)-**2h**		35[b]
2	**1i**		12	(±)-**2i**		64[c]
3	**1j**		12	(±)-**2j**		86
4	**1k**		12	(±)-**2k**		84

[a] Isolated yields of the α-bromo-β-azido carbonyl compounds **2** after column chromatography.
[b] 55% of starting chalcone **1h** was recovered.
[c] 28% of starting methyl cinnamate **1i** was recovered.

acts very slowly with NBS and $TMSN_3$ and after 12 h, a 1:1 mixture of bromoazide **2a** and dibromide **3a** was obtained in poor yield (Table 1, entry 1). When substrate **1a** was treated with 0.05 equiv of $Zn(OTf)_2$, 1.2 equiv of NBS and 1.5 equiv of $TMSN_3$ in CH_2Cl_2 at 0 °C for 10 min, bromoazide **2a** was obtained regioselectively in 85% yield (entry 7).

Various alkenes were subjected to the catalytic bromoazidation reaction (Table 2).[14,15] In all the cases, the reactions were *anti*-selective as revealed by the ^1H NMR of the crude products.

α,β-Unsaturated carbonyl compounds represent a synthetically useful class of substrates for various alkene oxidative reactions. In particular, bromoazidation of α,β-unsaturated carbonyl compounds would provide functionalized azidobrominated compounds, which could be transformed into various useful organic compounds by replacing the bromine atom with a series of nucleophiles and where the azido functionality would serve as a protected amino group. However, haloazidation of α,β-unsaturated carbonyl compounds has been poorly investigated. When chalcones and cinnamates were subjected to the $Zn(OTf)_2$ catalyzed bromoazidation reaction with NBS and $TMSN_3$ at 45 °C, *anti*-α-bromo-β-azido carbonyl compounds were obtained with moderate to good yields (Table 3).[16,17] At 0 °C or rt, the bromoazidation reaction of α,β-unsaturated carbonyl compounds was found to be very slow.

In conclusion, we have developed a new metal triflate catalyzed 1,2-bromoazidation of alkenes using NBS and $TMSN_3$ as the bromine and azide sources, respectively. $Zn(OTf)_2$ was found be the best catalyst. This catalytic method provides stereoselectively *anti*-1,2-azidobrominated products from a variety of alkenes including α,β-unsaturated carbonyl compounds.

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14. *General procedure*: To a well stirred suspension of substrate **1** (0.50 mmol) and 4 Å MS (0.100 g) in dry CH_2Cl_2 (2.5 mL) was added $Zn(OTf)_2$ (0.009 g, 0.025 mmol) under argon. The reaction mixture was cooled to 0 °C. $TMSN_3$ (0.1 mL, 0.75 mmol) and NBS (0.107 g, 0.60 mmol) were successively added. On completion (TLC), the reaction was quenched with aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The bromoazide product was purified by flash column chromatography using petroleum ether–EtOAc as an eluent.
15. All the compounds listed in Table 2 were characterized by ^1H NMR, ^{13}C NMR and FT-IR spectroscopy. Spectral data of compound (±)-**2d** were compared with the literature data.[7]
    Representative spectral data of bromoazide (±)-**2c**: Oily liquid; IR ($CHCl_3$, cm^{-1}): 2101 (N_3); ^1H NMR (200 MHz, $CDCl_3$): δ 2.11–2.30 (m, 1H), 2.35–2.55 (m, 1H), 2.80–3.20 (m, 2H), 4.42–4.51 (m, 1H), 4.74 (d, $J = 4.5$ Hz, 1H), 7.10–7.38 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9, 27.8, 50.3, 65.1, 126.6, 128.7, 129.1, 129.7, 130.5, 135.3.
16. *General procedure for chalcones and cinnamates*: To a well stirred suspension of chalcone or cinnamate **1** (0.50 mmol) and 4 Å MS (0.100 g) in dry CH_2Cl_2 (2.5 mL) were successively added $Zn(OTf)_2$ (0.009 g, 0.025 mmol), $TMSN_3$ (0.1 mL, 0.75 mmol) and NBS (0.107 g, 0.60 mmol) under argon. The reaction mixture was heated (45 °C) under reflux. The reaction was monitored by TLC and upon completion was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The bromoazide product was purified by flash column chromatography using petroleum ether–EtOAc as an eluent.
17. All the compounds listed in Table 3 were characterized by ^1H NMR, ^{13}C NMR and FT-IR spectroscopy.
    Representative spectral data of α-bromo-β-azido carbonyl compound (±)-**2j**: Gummy liquid; IR ($CHCl_3$, cm^{-1}): 2108 (N_3), 1745 (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.87 (s, 3H), 4.27 (d, $J = 10.7$ Hz, 1H), 4.91 (d, $J = 10.7$ Hz, 1H), 6.94 (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 46.0, 53.2, 55.1, 66.7, 114.1 (2C), 126.9, 129.1 (2C), 160.2, 168.5.